Final synopsis of Ph.D. thesis entitled

DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL SULFONAMIDE DERIVATIVES

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1. Objectives

The objectives of the research work entitled "***Design, Synthesis and Biological Evaluation of Some Novel Sulfonamide Derivatives***" include:

a) Design and synthesis of a series of novel sulfonamide derivatives with diverse chemical structures with potentially improved pharmacological properties
b) Structure elucidation of molecules using various analytical techniques
c) Screening (*in vitro*) of biological activities, such as antitubercular, antimicrobial, antioxidant, carbonic anhydrase inhibitory, and anticancer activity
d) Investigating the structure-activity relationship (SAR) between the chemical structures of the synthesized sulfonamide analogues and their biological activities
e) Performing computational *in silico* ADME study to predict the pharmacokinetics, and bioavailability of a drug candidate and molecular docking study to elucidate the potential binding modes of the compound with their biological targets, providing insights into activity

2. Statement of the Research Problem

The treatment of various diseases, including cancer, tuberculosis, and microbial infections, continues to be a significant challenge due to problems such as drug resistance and the limited efficacy of existing treatments. There is an ongoing demand for the development of novel therapeutic agents with improved efficacy and reduced adverse effects. This research addresses this gap by focusing on the design, synthesis, and biological evaluation of some novel sulfonamide derivatives due to their broad spectrum of pharmacological activities. These derivatives are intended to exhibit enhanced activities against target diseases, potentially offering new treatment options.

3. Nature and Scope of the Work Done

Literature review: The literature survey revealed that sulfonamide derivatives play a crucial role in medicinal chemistry due to their diverse spectrum of bioactivities and structural versatility. Currently, more than 150 FDA-approved drugs containing sulfonamide moiety are available in the market and many lead compounds with sulfonamide functionality also are in clinical tests for the treatment of different medical conditions.[1] The sulfonamide functionality possesses a diverse spectrum of bioactivities such as oral diuretics, anticancer, carbonic anhydrase inhibitors, antibacterial, anti-fungal, anti-Alzheimer, anti-TB, antidiabetic, antiviral, anti-inflammatory, *etc*.[2] Despite their potential, there remains a need to develop novel sulfonamide drug candidates that exhibit enhanced biological activities and improved pharmacokinetic profiles, thereby addressing unmet medical needs and advancing the field of medicinal chemistry.

Present work: The current research work begins with the rational design of novel sulfonamide derivatives based on existing knowledge. The novel target molecules were designed using molecular hybridization techniques, which involve merging different biologically active molecules through chemical modifications within a single framework that enhances the biological properties of the resulting molecule. The different bioactive heterocyclic pharmacophores like benzisoxazole, L-proline, piperazine, piperidine, benzofuran, pyrazole, oxime, imine, and sulfonamide functionality were clubbed in a single framework to enhance the biological activity of the newly synthesized molecules. The synthesized sulfonamide derivatives are well characterized and subjected to comprehensive biological evaluation to assess their pharmacological potential such as *in vitro* antitubercular, antimicrobial, antioxidant, carbonic anhydrase inhibitory, and anticancer activities.

Overall, the nature and scope of the work encompassed in the title involve a combination of synthetic organic chemistry, medicinal chemistry principles, and pharmacological evaluations aimed at the discovery and development of novel sulfonamide derivatives with potential therapeutic applications.

4. Research Methodology

Various research methodologies utilized to achieve the objectives of the research work are;

a) Utilized search engines like SciFinder, Reaxys, and databases like PubMed, Scopus, and Google Scholar to collect and analyze relevant articles, reviews, and patents
b) Designed novel sulfonamide derivatives using molecular hybridization methodology and based on structure-activity relationship (SAR) studies
c) Utilized various classical and advanced synthetic methods for stepwise synthesis of target sulfonamide derivatives
d) Structure elucidation using techniques like infrared spectroscopy (IR), ^{1}H nuclear magnetic resonance spectroscopy (^{1}H NMR), ^{13}C NMR spectroscopy, electrospray ionization mass spectrometry (ESMS), and elemental analysis
e) Evaluation of Anti-TB activity by Microplate Alamar Blue Assay (MABA), anticancer activity by using 3-(4, 5-dimethyl-2-thiazolyl)-2, 5-diphenyl-tetrazolium bromide (MTT assay), antioxidant activity using 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay, Antibacterial and Antifungal activity by Minimal inhibitory concentration (MIC) determination using standard agar dilution method, Carbonic anhydrase inhibitory potential using stopped-flow carbon dioxide hydrase assay
f) Computational tools for *in silico* ADME (Drug likeness) prediction using SwissADME and pharmacokinetic property via pkCS servers, molecular docking using AutoDock software

5. Contribution Made to the Existing Knowledge

Considering the significance of heterocyclic classes of compounds, we have synthesized various series of different sulfonamide analogues and screened for their antitubercular, antimicrobial, antioxidant, anticancer, and carbonic anhydrase inhibitory activity in search of novel drug candidates that might possess improved efficacy and therapeutic properties. The research findings suggest that synthesized sulfonamide analogues can serve as important templates for the development of molecules aimed at combating drug-resistant strains or targets, contributing to the ongoing effort of drug discovery to meet the unmet medical needs of human life-saving treatments.

The developed synthetic protocols and results of preliminary biological screening of novel sulfonamide derivatives can serve as a valuable educational resource for knowledge among scientists and researchers, fostering collaboration and inspiring further research in drug development.

6. Organization of Thesis

The present research work carried out during my tenure has been combined as a thesis entitled "***Design, Synthesis and Biological Evaluation of Some Novel Sulfonamide Derivatives***." This work has been broadly divided into seven chapters.

Chapter 1: Introduction

This chapter briefly describes the background and discovery of heterocyclic compounds containing a sulfonamide functional group. Heterocyclic compounds are crucial players in the intricate biochemical processes within our bodies, serving as essential blueprints in medicinal chemistry for developing diverse therapeutic agents. The synthesis of new compounds stands as a cornerstone of organic chemistry, driving advancements across different scientific disciplines. Particularly, heterocycles infused with nitrogen and sulfur exhibit a plethora of uses in medicinal chemistry, showcasing their versatility and significance in pharmaceutical innovation.[3]

Chapter 2: Literature Survey

This chapter explores several synthetic techniques and highlights the broad spectrum of biological activity associated with different sulfonamide derivatives. The synthetic methods involve the classical and various advanced approaches. The classical approach of synthesis involves the reaction of sulfonyl chloride and amino compound in the presence of a base. However, researchers have developed various advanced and more efficient synthetic methods that utilize environmentally benign conditions. Numerous powerful methods[4] have been reported for the synthesis of sulfonamides, including microwave and ultrasonic-assisted synthesis, transition-metal-catalyzed synthesis, flow-based technology, solid-phase synthesis, and the use of water or ionic liquids, nanocatalysts, etc.

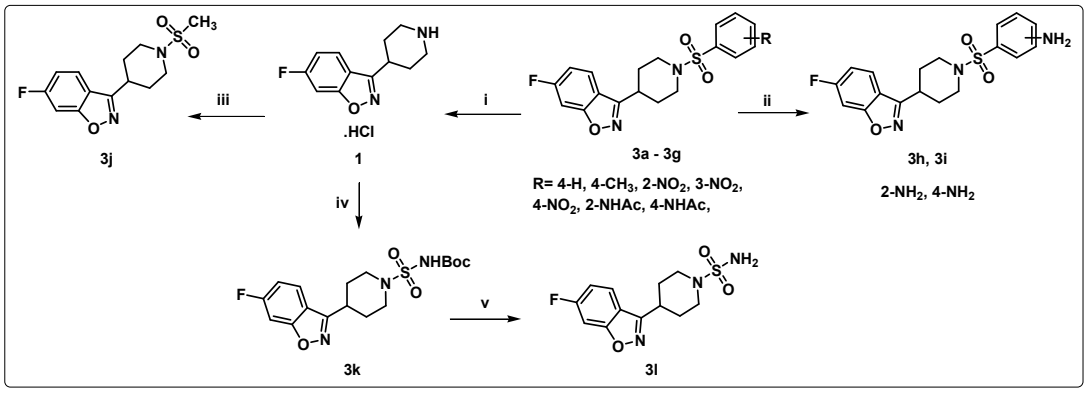
The sulfonamide functional group has been an important motif in medicinal chemistry due to a wide array of bioactivities such as antibacterial, antifungal, anti-inflammatory, anticancer, antioxidant, carbonic anhydrases, antidiabetic, antiviral, and antitubercular.[5,6] The sulfonylpiperazine/piperazine sulfonamide-based analogues are reported for a broad spectrum of activities.[7]

Keeping in view, the importance of these heterocyclic classes of compounds, we have planned the synthesis of a series of sulfonamide derivatives containing biologically important pharmacophores and screened for their antitubercular, antimicrobial, antioxidant, anticancer activities, hCA inhibitory activity along with molecular docking, and *in silico* ADME study.

Chapter 3: Synthesis, Biological Evaluation, and Computational Studies of Benzisoxazole Sulfonamide Conjugates

This chapter details the synthesis and biological evaluation of a small focused library of 6-fluoro-3-(piperidine-4-yl)benzo[*d*]isoxazole sulfonamide hybrids. These newly synthesized compounds were assessed for their *in vitro* anticancer (A-549, HCT-116, and VERO cell lines) and anti-TB activities; computational studies were conducted to corroborate the experimental findings. Benzisoxazole derivatives are versatile molecular frameworks that serve as the basis for a wide array of compounds targeting various biological activities such as anti-HIV, antimicrobial, anticonvulsant, anticancer, antidiabetic, anti-inflammatory, antioxidant, antipsychotic, acetylcholine esterase, and analgesic agents.[8] The target sulfonamide derivatives were synthesized using scrutinized optimal reaction conditions with yields ranging from 80% to 85% (**Scheme 1**).

Scheme 1. Synthetic route for the sulfonamide derivatives **3a-3l**



Reagents and conditions: (**i**) **1**, DMF, 15 °C then K_2CO_3, benzenesulfonyl chloride, 65 °C, 2 h; 78-89% (**ii**) Fe/HCl, Ethanol: H_2O (1:1), 80 °C, 10 h, 76-78%; (**iii**) **1**, DCM, TEA, methanesulfonyl chloride, 10 °C to RT, 10 h, 86%; (**iv**) *t*-Butanol, DCM, 0 °C, chlorosulfonyl isocyanate, 0.5 h then **1**, TEA, 1h to RT, 2 h, 82%; (**v**) DCM, TFA, 0 °C to RT, 2 h, 85%

The preliminary *in vitro* screening for antimycobacterial activity against *Mycobacterium tuberculosis* (*Mtb*) *H37Rv* revealed that compounds **3a** and **3b** demonstrated moderate anti-TB

potential with an IC_{50} value of 25µM. Moreover, compounds **3a** and **3b** exhibited moderate activity against MCF-7 and HCT-116 cell lines with IC_{50} values of 37.50 µg/mL and 41.36 µg/mL, respectively. Furthermore, sulfonamide hybrid **3b** exhibited better antioxidant activity with an IC_{50} value of 61.84µM as compared to ascorbic acid (IC_{50}: 128.15µM). The molecular docking study targeting cyclin-dependent kinase 8 (CDK8) as a possible target for anti-cancer activity revealed that most of the compounds exhibited favorable binding affinities (-8.7 to -10.3 kcal/mol) against CDK8 (**PDB 6T41**) as compared to standard fluorouracil. All synthesized compounds ensure their structural integrity and purity. Furthermore, these compounds demonstrate favorable ADME properties, aligning with Lipinski's rule of five and indicating their potential as drug candidates.

Chapter 4: Synthesis and Biological Evaluation of *N*-(arylsulfonyl)-L-proline-piperazine Derivatives

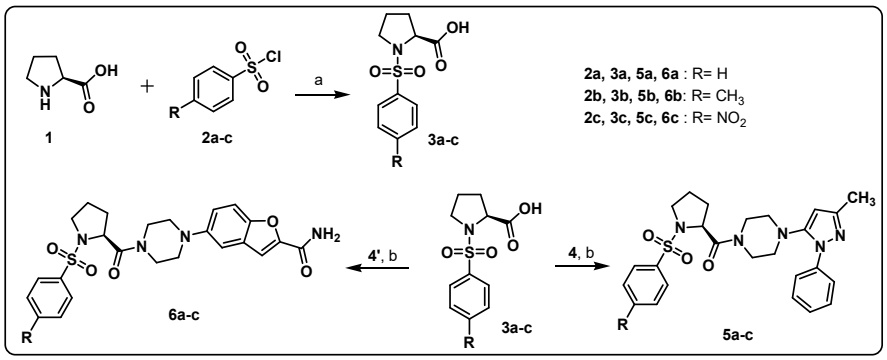
We have designed and synthesized a novel series of *N*-(arylsulfonyl)-L-proline derived hybrids tethered with pharmacologically attractive cores such as 1-(3-Methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazine and 5-(Piperazin-1-yl)benzofuran-2-carboxamide. Piperazine is a privileged six-membered nitrogen-containing heterocyclic core due to its diverse pharmacological activities.[9] Among the different amino acids, L-proline is an extensively studied amino acid due to its numerous pharmacological and biotechnological applications. The *N*-functionalization of amino acids has limitless uses in medicinal research. The substituted proline derivatives possess versatile biological activities[10] like antibiotics, anti-hepatitis, antidiabetic, antihypertensive, antiarrhythmic, antiprotozoal, analgesic, antibacterial, *etc*.

These new derivatives were synthesized using L-proline (**1**) as readily available raw materials. These novel molecules were assessed for *in-vitro* antimicrobial activity against a panel of six different representative human pathogenic strains *viz*, *Staphylococcus aureus*, *Bacillus subtilis* (Gram-positive), and *Escherichia coli, Pseudomonas aeruginosa* (Gram-negative), as well as *Candida albicans* and *Aspergillus niger* (fungal strains). The two-step synthesis of the target molecules (**Scheme 2**) involves the preparation of *N*-arylsulfonyl-L-proline scaffolds from L-proline and various sulfonyl chlorides followed by EDC.HCl/HOBt mediated amide coupling with 80-85 % yield. The reduction of the nitro group followed by *N*-acetylation afforded other corresponding derivatives (**Scheme 3**).

The amino-substituted analogue **5d** elicited a lower MIC value (104 µg/mL) against *Bacillus subtilis* whereas, derivative **5e** with *N*-phenylpyrazolyl units displayed a significant MIC value of 107 µg/mL against gram-positive *Staphylococcus aureus* than the standard ampicillin (MIC: 250 µg/mL). The compound **5b** exhibited equipotent antioxidant activity with an IC_{50} value of 19.25 µg/mL compared to standard BHT (IC_{50}: 16.47 µg/mL). The molecular docking results

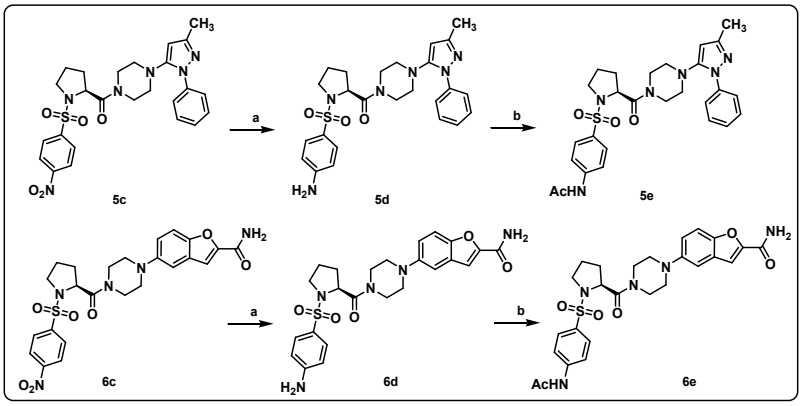
against the active site of receptor *S. aureus* tyrosyl-tRNA synthetase disclosed the noteworthy correlation between the predicted binding energies and experimental antibacterial activities.

Scheme 2. Synthetic pathway of the sulfonamide derivatives (**5a-c** and **6a-c**)



Reagents and conditions: (a) Na_2CO_3, H_2O, 0 °C to RT, 5 h, 89-92%; (b) EDC.HCl, HOBt, DIPEA, DMF, RT, 6 h, 80-84%

Scheme 3. Synthetic pathway of the sulfonamide derivatives (**5d-e** and **6d-e**)



Reagents and conditions: (a) Zn/NH_4Cl, H_2O, 60 °C, 6 h, 70-73%; (b) CH_3COCl, TEA, DCM, 0-5 °C, 2 h, 75-78%

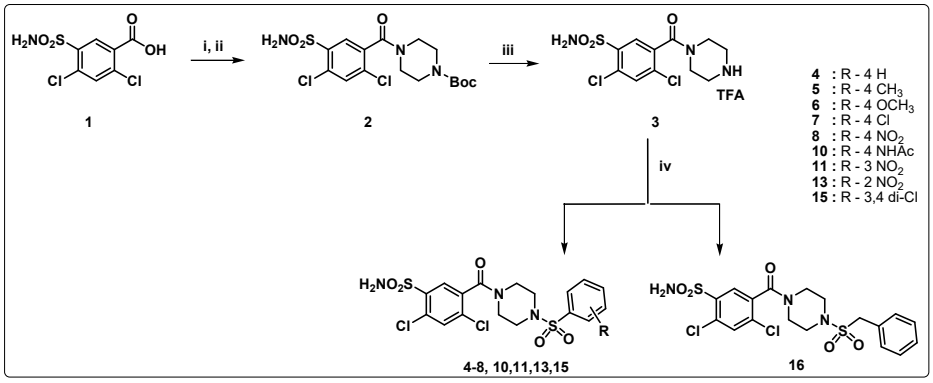
Chapter 5: Design and Synthesis of Novel Series of Sulfonylpiperazine Containing 2,4-Dichlorobenzenesulfonamides as Carbonic Anhydrase Inhibitors

This study involves the synthesis and evaluation of the hCA activity of a focused library of thirteen novel sulfonylpiperazine containing 2,4-dichlorobenzenesulfonamides derivatives. These compounds were evaluated for their inhibitory effects against two human cytosolic carbonic anhydrases (hCA I and hCA II) as well as two tumor-associated membrane carbonic anhydrase isozymes (hCA IX and hCA XII). CA are metalloenzymes that play a pivotal role in numerous physiological functions including pH regulation, ion transportation, bone resorption, CO_2 homeostasis, and respiratory functions. Several benzenesulfonamide derivatives are reported as CAIs for tumor-associated hCA IX, and XII isoforms.[11]

The synthesis of new molecules is achieved through a four-step process, as depicted in **Scheme 4**. The coupling reaction between the commercially available starting materials, 2,4-Dichloro-5-sulfamoylbenzoic acid (**1**) and *tert*-butyl piperazine-1-carboxylate (*N*-Boc-piperazine), was accomplished using the conventional method of preparing acid chloride from acids.

Subsequent deprotection of the Boc derivative **2** using TFA affords **3**, which on reaction with various sulfonyl chlorides, afforded the designed benzenesulfonamide analogues.

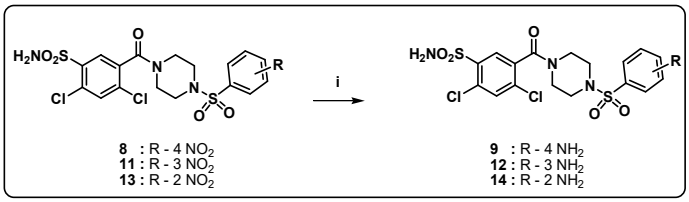
Scheme 4. Synthetic pathway of the sulfonamide derivatives **4-8**, **10**, **11**, **13**, **15** and **16**



Reagents and conditions: (i) $SOCl_2$, toluene, 10 ° C to 45 °C, 6 h; (ii) *N*-Boc piperazine, TEA, THF, 5 °C to RT, 5 h, 68% (over 2 steps); (iii) DCM, TFA, 5 °C to RT, 2 h, 72%; (iv) DMF, K_2CO_3, 15 °C, RSO_2Cl, RT, 5 h, 77-84%

The reduction of the nitro group of compounds (**8**, **11**, and **13**) was achieved by iron powder/aq. HCl in a mixture of ethanol and water at 75 °C to get corresponding amino derivatives (**9**, **12**, and **14**, respectively) as shown in **Scheme 5**.

Scheme 5. Synthetic pathway of the sulfonamide derivatives **9**, **12** and **14**



Reagents and conditions: i) Fe powder/aq. HCl, EtOH: H2O (1:1), 75 °C, 3h

Among the series reported, compounds **7** and **9** fulfilled the kinetic profile and solubility requirements necessary to be considered in the *in vivo* model of intraocular pressure (IOP). The obtained results sustained that derivative **9** was far more effective and long-lasting than the reference drug **AAZ** in lowering the IOP. Moreover, 2-amino sulfonamide hybrid **14** displayed the highest activity against transmembrane hCA IX isoform, with a K_I value of 11.4 nM, and benzyl analogue **16** elicited potent activity against hCA XII isoform with a K_I value of 0.87 nM, respectively.

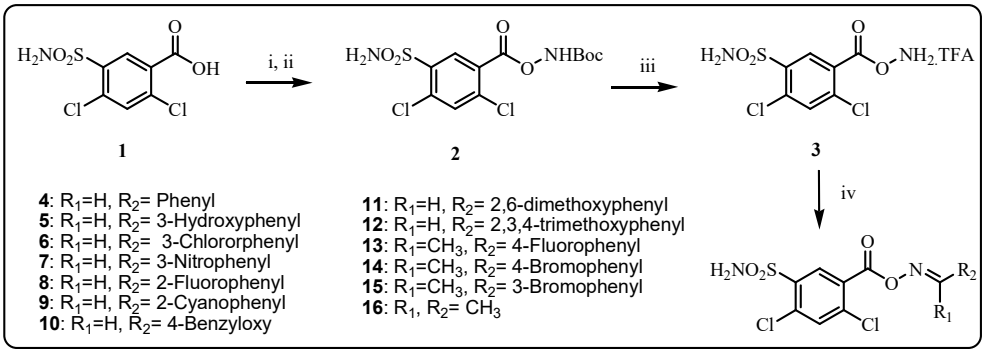
<u>Chapter 6</u>: Synthesis and Evaluation of Carbonic Anhydrase Inhibitory Potential of Oxime Ester Derivatives of 2,4-Dichloro-5-sulfamoylbenzoic acid

In search of novel carbonic anhydrase inhibitors, we have synthesized a novel series of oxime ester derivatives of 2,4-Dichloro-5-sulfamoylbenzoic acid through a molecular hybridization approach containing primary sulfonamide and imine functionalities in a single framework. The CA inhibitory activity was assessed against carbonic anhydrase isoforms hCA I, II, IX, and XII in comparison to

acetazolamide. For years, Schiff bases/imines (–C=N–) have been greatly inspiring to many chemists and biochemists due to their diverse activities.[12] Schiff bases/hydrazone derivatives have been synthesized through the condensation of different aldehydes or ketones with amines.

As shown in **Scheme 6**, oxime ester derivatives of lasamide with imine backbone (**4-16**) were prepared by reacting intermediate **3** with sodium acetate and appropriate aldehyde/ketone in ethanol at 75 °C. Intermediate **3** was prepared from commercially available starting materials such as 2,4-Dichloro-5-sulfamoylbenzoic acid (**1**) and *N*-Boc hydroxylamine.

Scheme 6. Synthetic route for sulfonamide derivatives (**4-16**)



Reagents and conditions: (i) $SOCl_2$, toluene, 10 ° C to 45 °C, 6 h; (ii) *N*-Boc hydroxylamine, TEA, THF, 5 °C to RT, 10 h, 71% (over 2 steps); (iii) DCM, TFA, 5 °C to RT, 5 h, 72%; (iv) Ethanol, sodium acetate, aldehyde/ketone, 75 °C, 5-6 h, 75-83%

All compounds (**1-16**) elicited inhibitory activity against cancer-related hCA IX isoform with K_I values in the range of 3.4-43.3 nM. The dimethoxyphenyl derivative **11** proved to be a highly effective inhibitor and selective for both the tumor-associated isoforms IX and XII with K_I values of 10.7 nM and 7.5 nM, respectively, and therefore, an *in silico* investigation was conducted to establish their binding modes. In addition, selected compounds **4**, **11,** and **12** showed interesting antiproliferative effects on human triple-negative breast cancer cell line MDA-MB-231. Hence, the findings of this work suggested that the oxime ester derivatives of lasamide **1** could lead to potential anticancer agents by targeting hCAs IX and XII.

Chapter 6: Conclusions and Future Scope

Conclusions: We have designed and successfully synthesized four distinct series of sulfonamide derivatives, as detailed in Chapters **3** through **6**, and assessed their therapeutic potential. Most of the synthesized compounds were purified by recrystallization/trituration without any need of column purifications. All newly synthesized molecules were obtained in pure form and thoroughly characterized using ^{1}H NMR, ^{13}C NMR, FTIR, ES-MS, and elemental analysis before their biological activity evaluation. This research work identified key structural features contributing to the biological activity such as antimicrobial, antitubercular, anticancer, carbonic anhydrase inhibitory, and/or antioxidant properties of sulfonamide derivatives.

Future Scope: (a) Future studies could focus on the incorporation of biologically relevant pharmacophores like indole, benzimidazole, benzothiazole, and triazoles instead of pyrazole/benzofuran in *N*-(arylsulfonyl)-L-proline-piperazine derivatives, that could lead to significant improvements in multi-targeted activity. (b) Synthesis of a novel series of sulfonylurea by modification in the head group in oxime ester derivatives of 2,4-Dichloro-5-sulfamoylbenzoic acid to develop molecules with enhanced anticancer and/or hCA inhibitory activity. (c) Future research, building on the foundations laid by this work, holds the promise of translating these novel sulfonamide derivatives from the hit to the lead, offering new hope for treatments in areas of unmet medical need.

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9. List of Publications/Conferences Attended

1) Kilbile, J. T., Tamboli, Y., Ansari, S. A., Rathod, S. S., Choudhari, P. B., Alkahtani, H., and Sapkal, S. B. (2023). Synthesis, biological evaluation, and computational studies of 6-fluoro-3-(piperidin-4-yl)-1, 2-benzisoxazole sulfonamide conjugates. *Polycyclic Aromatic Compounds*, 1-21. https://doi.org/10.1080/10406638.2023.2247117

2) Kilbile, J. T., Ansari, A. S., Gadekar, S. S., Vagolu, S. K., Damale, M. G., Kashid, B. B., Sangshetti, J. N. and Sapkal, S. B. (2024). Design, synthesis, and molecular docking study of *N*-(arylsulfonyl)-L-proline-piperazine hybrids tethered with pyrazole/benzofuran moiety as antimicrobial agents. *Synthetic Communications*, *54(7)*, 567-582. https://doi.org/10.1080/00397911.2024.2320856

3) Kilbile, J. T., Tamboli, Y., Gadekar, S. S., Islam, I., Supuran, C. T., and Sapkal, S. B. (2023). An insight into the biological activity and structure-based drug design attributes of sulfonylpiperazine derivatives. *Journal of Molecular Structure*, *1278*, 134971. https://doi.org/10.1016/j.molstruc.2023.134971

4) Kilbile, J. T., Gadekar, S. S., and Sapkal, S. B. Exploring the Green Approach of Ionic Liquids for Synthesis of Sulfonamides; *National Conference on Recent trend in Chemical Sciences Research (RTCSR-2024)* at Balbhim College, Beed, Date: 20 January 2024 (Paper ID: 59).

5) Kilbile, J. T., Tamboli, Y., Gadekar, S. S., and Sapkal, S. B. Synthesis, Biological Assessment, and Computational Studies of Novel Piperazine-proline Sulfonamide Derivatives; *National Conference on Exploring New Horizons In Forensic Chemical And Biological Sciences* at Government Institute of Forensic Science, Chhatrapati Sambhajinagar, Date: 29 February 2024

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